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11

EXAMINER
GAKH, YELENA G

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1743	

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Please find below and/or attached an Office communication concerning this application or proceeding.

DETAILED ACTION

1. The Amendment and Declaration, filed on 04/04/03, are acknowledged. Claims 1-33, 35-36, 38-41, 46-48 and 50-80 are pending in the application.

Specification

2. The specification is objected to as using terminology, which contradicts conventional meaning of the terms and thus leads to misinterpretation of the essence of the invention.

The specification discloses generating different crystal forms of polymorphs in capillary spaces, including capillary tubes. The specification indicates that "there are several factors that discourage the use of capillary tubes for solidifying compounds or mixtures" (page 8, lines 24-26), the statement supported with reasonable arguments. However, description of the capillary spaces (or tubes), given in the specification, completely contradicts conventional meaning of this term, which can be found, for example in Chemistry Dictionary: "a capillary is a tube having **a very small inside** diameter" (Onelook on-line dictionaries), i.e.: a "'capillary space' is defined herein to mean a space having walls separated by from about 0.1 mm to about 30 mm" (page 15, lines 1-3), in other words, the diameter of the "capillary space" according to this definition reaches 3 cm. Tubes (or 'capillary spaces' surrounded by walls) with inner diameter of 3 cm are not the capillaries. Even 5 mm tubes, routinely used in NMR experiments, are not considered to be "capillaries", because such phenomenon as "capillary forces" acting on liquids in the capillary tubes, is not applicable to the tubes of such diameter. Moreover, the "capillary spaces" with diameters over 4 mm are conventionally used in laboratories for solidifying (crystallizing) samples. It would have been obvious for anyone of ordinary skills in the art to use tubes of such diameters for crystallizing samples, unlike real capillaries.

Claim Objections

3. Claim 1 is objected to because of the following informalities: it recites "disposing the sample **on** one or more receptacles" and "solidifying the sample **on** the receptacle", which may

be interpreted as disposing it on the outside surface of the receptacles; however, disposing the sample **in** the receptacles is recited further. Appropriate correction is required.

Claims 68 and 70 obviously have a wrong dependency. The examiner will interpret them as depending on claims 67 and 69, respectively, which recite a melt.

Claim 80 contains grammatical error: "comprises is a well plate". Correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-33, 35-36, 38-41, 46-48 and 50-65 and 67-80 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "classifying said at least one solid form", which is an indefinite and unclear step. Which classes are meant here? Is classifying of the form performed according to the classification table of the solid forms? Then the step of comparing the generated form with those known from classification table is required. Is discerning between crystal and amorphous solid forms of the sample considered to be its classification? The examiner interprets this step in this last meaning.

The third step of analyzing the form is also indefinite. What is "the manner wherein the analytical result is indicative of the generated solid form"? Can visualizing the formation of crystals versus non-crystal forms be considered analyzing them?

Claims recite a method of screening for possible solid forms by disposing the sample in receptacles, at least one of which defines a capillary space. As it was indicated above, the capillary space defined in the specification contradicts the conventional meaning of this term; specifically claims 62-65 recite the upper limit of the diameter of these spaces (as the vague definition of 'capillary spaces' measured in cm, can be interpreted) up to 30, 17, 7 and 5 mm. Such language of the claims leads to their misinterpretation. Since the definition of the "capillary spaces" given in the specification actually includes routine lab receptacles, the

examiner will interpret the claims in the broadest scope disclosed in the specification and will consider these receptacles to be conventional glassware used for crystallization of samples.

In this respect, claim 5 is not clear, as it is not apparent, what is defined as "a receptacle that does not define a capillary space".

In claim 12 it is not clear what serves as receptacles in the case of a sheet with holes or pores – the holes? With the holes of up to 3.cm? How can they serve as receptacles?

Claim 11 recites a "capillary tube". Does it have the same "capillary space" as the one defined in the specification? Since no definition is given for the capillary tube, the examiner considers the "capillary tube" being a real capillary, which excludes such tubes as e.g. NMR tubes with inner diameter of 5 cm.

Claim 23 is not clear. Is it supposed to recite rotating a capillary **around** (or **about)** (rather than *along*) its own axis?

Claims 28 and 33 are not clear. Which "one end" of the receptacle is closed, if the receptacle actually has a bottom wall? Is this the same end, i.e. the bottom of the receptacle?

Claim 31 is not clear. Shouldn't it be a dependent claim from claim 30, reciting, "wherein concentrating the solid or semisolid is sufficient to facilitate in-situ analysis", since otherwise it is not clear, how evaporation can facilitate the analysis?

Claim 32 is completely not clear. What "environmental variation" is meant here? Is this the variation of conditions inside the receptacle? Outside the evaporator?

Claims 53-56 lack clarity, as it is not apparent, what is the sample being screened for? Besides, the claims have the deficiencies indicated above for claim 1.

In claim 67 it is not clear what "element" is meant here, and how it s possible to have a mixture of "a compound" and "an element". Is this an element form the Periodic Table?

The language of claims 77 and 80 renders the definition of "one receptacle" indefinite. If **one** receptacle **is** a **multi**-well plate, than what would be actually one receptacle? Such definition contradicts previous definitions of one receptacle as e.g. one capillary and renders the claims unclear and indefinite.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. **Claims 1-6, 8-9, 12-14, 17, 35-36, 40, 50-52, 57-60, 62-64 and 71-80** are rejected under 35 U.S.C. 102(e) as being anticipated by Lehmann (US 6,507,636 B1).

Lehmann discloses a "rapid X-ray diffraction screening method of polymorph libraries created in multi-well plates" (Title): "method and device for rapid characterization of arrays of crystalline, polycrystalline or amorphous materials; in particular for the formation and X-ray diffraction analysis of polymorph libraries and the discovery of new crystal forms. According to one aspect, a multi-well plate comprising a masking plate with an array of openings and a removable base plate is used to crystallize precipitates. X-ray diffraction analysis is performed by scanning an X-ray beam over the base plate and recording diffractograms of the crystalline precipitates" (Abstract). "Arrays of crystalline or polycrystalline precipitates are created by depositing a solution containing the dissolved substance to be crystallized in one well of the multi-well plate. Further wells are filled with the same substance dissolved either in the same solvent at a different concentration or in a different solvent or mixture of at least two different solvents. By changing at least one crystallization parameter either continuously with time and or space, or changing at least one crystallization parameter suddenly, crystallization is initiated and allowed to progress. Crystallization parameters include but are not limited to, change of solubility of the substance by change of concentration of the substance in solvent through solvent evaporation; change of solubility of the substance by adding precipitant; change of solubility of the substance through change of temperature. *In one embodiment the rate of evaporation is controlled by differently sized apertures fixed to the top site of the multi-well plate*" (col. 5, lines

48-65). "Different sized apertures fixed on the top site of the multi-well plate" provide different types of receptacles. Adding precipitant provides a mixture of compounds in the receptacles.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. **Claims 7, 15 20-21, 38-39, 41 and 61** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann.

Although Lehmann does not specifically disclose at least 100 receptacles, the multi-well plates with over 96 wells are well known in the art, and it would have been obvious to use any

commercially available multi-well plates to perform Lehmann's method, especially with higher number of wells, because this leads to increased efficiency of the method.

Although Lehmann does not specifically teach comparing the generated solid form to a known form, or screening a known polymorph or unknown but potential polymorph, it would have been obvious for anyone of ordinary skills in the art to perform steps of claims 20-21 and 38-39, because searching for new polymorph forms of the solids by comparing them with the known forms, with performing the same method for these known forms as a preliminary step, is an exact aim of Lehmann's method.

Although Lehmann does not specifically include the step of analyzing the polymorph for its bioavailability, it is notoriously well known in the art that different polymorphs of a pharmaceutical have different bioavailabilities based, among other factors, on their solubility, which is mentioned by Lehmann in the Background of the Art. The goal of screening pharmaceutical polymorphs for their different solid forms is obtaining the best candidate, which includes its bioavailablity. Therefore, it would have been obvious for anyone of ordinary skill in the art to add the step of determining bioavailability of the polymorph in Lehmann's method.

Although Lehmann does not specifically disclose synchrotron radiation as the radiation source in X-ray analysis, this technique is notoriously well known in the art, has obvious benefits of a tunable X-ray source, and it would have been obvious to use it in Lehmann's method.

11. **Claims 16 and 47** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann in view of Gu et al. (J. Pharmac. Sci., IDS).

Lehmann does not teach Raman spectroscopic analysis in his method.

Gu teaches characterization of polymorphic forms of the sample using FT Raman spectroscopy.

It would have been obvious for anyone of ordinary skill to use FT Raman scattering analysis instead of X-ray analysis in Lehmann's method, because Gu emphasizes that "FT-Raman technique is more suitable for studying certain polymorphs" (Introduction).

12. **Claims 10-11, 18-19, 46, 48 and 66** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann in view of Hol (US 6,267,935 B1).

Lehmann does not particularly teach placing the sample into at least one capillary tube and forming supersaturated solution of the sample.

Hol discloses a crystallization media for crystallizing proteins and other molecules especially macromolecules, in crystallization plates, comprising capillaries of 0.5-1 mm in diameter with formation of supersaturated solution (Abstract, col. 10, lines 51-56). The process of crystallization is monitored with X-ray diffractometer.

It would have been obvious for anyone of ordinary skills in the art to include capillaries in Lehmann's method for growing crystal forms of macromolecules and characterize them by X-ray analysis, as taught by Hol, because this expands Lehmann's method to generating more crystal forms when screening polymorphs of natural products. Supersaturated solution is formed in the capillaries disclosed by Hol.

Although Lehmann in view of Hol do not specifically disclose synchrotron radiation as the radiation source in X-ray analysis, this technique is notoriously well known in the art, has obvious benefits of a tunable X-ray source, and it would have been obvious to implement it in Lehmann's method.

13. **Claims 10-11, 18, 22-33 and 53-56** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann in view of Schuler or Sibille et al. (J. Crystal Growth, IDS).

Lehmann does not specifically disclose using capillaries and centrifuging them during the process of crystallization.

Schuller teaches crystallizing chromogenes in capillaries indicating that obtaining crystal versus amorphic forms depends on the conditions "under which the solvent is evaporated", however that such conditions are difficult to maintain and to make the results reproducible. He indicates that freeze-drying is not suitable for capillaries because it is hard to keep cold temperatures. However, he did not indicate that there are any difficulties in using centrifuging under vacuum for evaporating solvent during crystallization.

Sibille teaches influence of solvent evaporation rates in the closed capillary on protein crystal growth.

It would have been obvious for anyone of ordinary skills in the art to use capillaries in Lehmann's method, as well as centrifuging them under various conditions, because this all changes the rate of evaporation of the solvent from the capillaries, which drastically changes the way of crystallization of the polymorph, thus creating its different forms, as indicated by Schuler and Sibille.

14. **Claims 67-70** are rejected under 35 U.S.C. 103(a) as being unpatentable over Lehmann in view of e.g. Brittain (Polymorphism in Pharmaceutiacl Solids, IDS).

While Lehmann does not specifically disclose solidifying a sample from a melt, rather than a solution, Brittain teaches using melt as a conventional choice for crystallizing polymorphs. Therefore, it would have been obvious for anyone of ordinary skills in the art to use melt, as disclosed by Brittain, instead of solution in Lehmann's method, because this is a conventional way of obtaining solid forms for polymorphs.

Response to Arguments

15. In their General Response to Prior Art Rejections and regarding claim 41 the Applicants indicate that the examiner agreed to allow amended claim 41 and that she came to the conclusion of allowability of the claimed method over the prior art. The examiner would like to emphasize that no allowable subject matter was indicated in the interview and apologize for such misunderstanding due to possible inaccurate formulation of her conclusions. In fact, the examiner agreed to reconsider the application in light of the material presented by the Applicants in the interview as an explanatory to the disclosure of the application. However, she would like to notice that contrary to the clear, precise and accurate presentation of the material in the interview, the present application has rather a broad and indefinite disclosure, which prevents the application from becoming allowable at this moment.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yelena G. Gakh, Ph.D. whose telephone number is (703) 306-5906. The examiner can normally be reached on 9:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill A. Warden can be reached on (703) 308-4037. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 872-9310 for regular communications and (703) 872-9311 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0661.

Yelena G. Gakh
June 30, 2003